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PD-L1 positive lympho-epithelial lesions in inflammatory prostate

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Summary. Objectives. Ductal epithelial changes (lympho-epithelial lesions-LEL) in prostatic chronic inflammation (CI) are not well studied so far.

Aim. To investigate LEL immediately adjacent to prostatic CI.

Methods. We studied LEL in 144 prostatic surgical and autopsy specimens in various types of prostatic CI: NIH-category IV prostatitis (histologic prostatitis-HP), nonspecific granulomatous prostatitis (NSGP), and the reactive lymphoid infiltrates in the vicinity of benign prostatic hyperplasia (BPH) and prostate adenocarcinoma (PCa). CI is scored as low and high grade (LG, HG) according to the severity of inflammation.

Results. LEL was identified in all types of prostatic specimens and in all types of prostatic CI: in 70.9% of patients with HP; in 100% of cases with NSGP; in 68.7% and in 80% adjacent to BPH and PCa respectively. Statistical analysis showed a significant correlation of the presence of LEL with HG CI ($p<0.001$). LEL showed strong membranous PD-L1 expression.

Conclusions. The study presents the first attempt to examine LEL in inflammatory human prostate. PD-L1 positive LEL have no diagnostic organ specificity, although they are a constant histological finding in HG prostatic CI. LEL, inducible after birth by CI, are an integral part of prostate-associated lymphoid tissue (PALT) and of the inflammatory prostatic microenvironment.

Key words: Prostatitis, Lympho-epithelial lesions, Inflammation, PD-L1, PALT

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Introduction

The term lympho-epithelial lesions (LEL) reflects the presence of distinct morphologic changes in ductal (often) or secretory epithelium in the glandular organs. The lesion is a classical histologic hallmark of both malignant (lymphoma of mucosa-associated lymphoid tissues - MALT), and benign inflammatory diseases with reactive or autoimmune pathogenesis (Matias-Guiu and Esquius, 1991; Daniels, 1992; Valdez et al., 2003; Isaacson et al., 2008; Giday et al., 2011). By definition, LEL are aggregates or clusters of three or more lymphoid cells with distortion or destruction of the epithelium, and morphological changes within epithelial cells including distinct eosinophilia (Isaacson et al., 2008). The use of cytokeratin immunostaining emphasizes the clusters of intra-epithelial lymphocytes (IEL) in the LEL as well. The epithelial ductal cells in LEL express MUC1 as diffuse cytoplasmic staining with apical accentuation (Taki et al., 2002; Sung et al., 2015).

Malignant LEL in marginal zone lymphomas are abundant, with destructive character and contain large, atypical centrocyte-like B-lymphoid cells (Isaacson et al., 2008; Pericart er al., 2020). In inflammatory diseases everywhere in the body, benign LEL are small, non-destructive, and contain mature IEL often with a predominance of T-cells (Daniels, 1992; Valdez et al., 2003; Isaacson et al., 2008; Giday et al., 2011).

Although in recent years there has been marked activity in the studies on chronic inflammation (CI), LEL in inflammatory prostate have not been described in the literature so far (De Marzo et al., 2007; Delongchamps et al., 2008; Sfanos et al., 2018).

The aim of this study was to investigate the presence and frequency of benign (non-lymphomatous) LEL in a large cohort of patients with different types of surgical and autopsy prostate specimens and in the most frequent socially important prostate diseases. These include National Institutes of Health (NIH)-category IV prostatitis or histologic prostatitis (HP), nonspecific

granulomatous prostatitis (NSGP), and reactive lymphoid infiltrates in the vicinity of benign prostatic hyperplasia (BPH), as well as prostate adenocarcinoma (PCa).

Materials and methods

A retrospective record review was performed on a large volume of prostatic material of all types: radical prostatectomies (RP), transurethral resection of the prostate and adenomectomies (TURP/AD), and autopsies at the Departments of General and Clinical Pathology of St. George University Hospital of Plovdiv, Bulgaria and the Grand Hôpital de l'Est Francilien, Jossigny, France. Prostatic needle biopsies were not examined because of the small amount of prostatic tissue available for histological analysis. The presence of LEL in a total of 144 cases was evaluated: 37 TURP/AD-specimens of patients with BPH, 9 selected TURP-specimens of patients with NSGP, 30 RP-specimens of patients with PCa, and 68 autopsy specimens of patients who had died from non-urological diseases.

The nine cases of NSGP were used in our previous study (Dikov et al., 2020) but were included here due to the LEL investigation. The autopsy prostates included 16 medico-legal cases of young men who died in traffic accidents with no documented illness and 6 prostates of new-borns and children in prepuberty.

Clinical and follow-up data were obtained from medical records, surgical pathology, and autopsy files. During the primary review of tissue samples and clinical records of the patients the following selection criteria

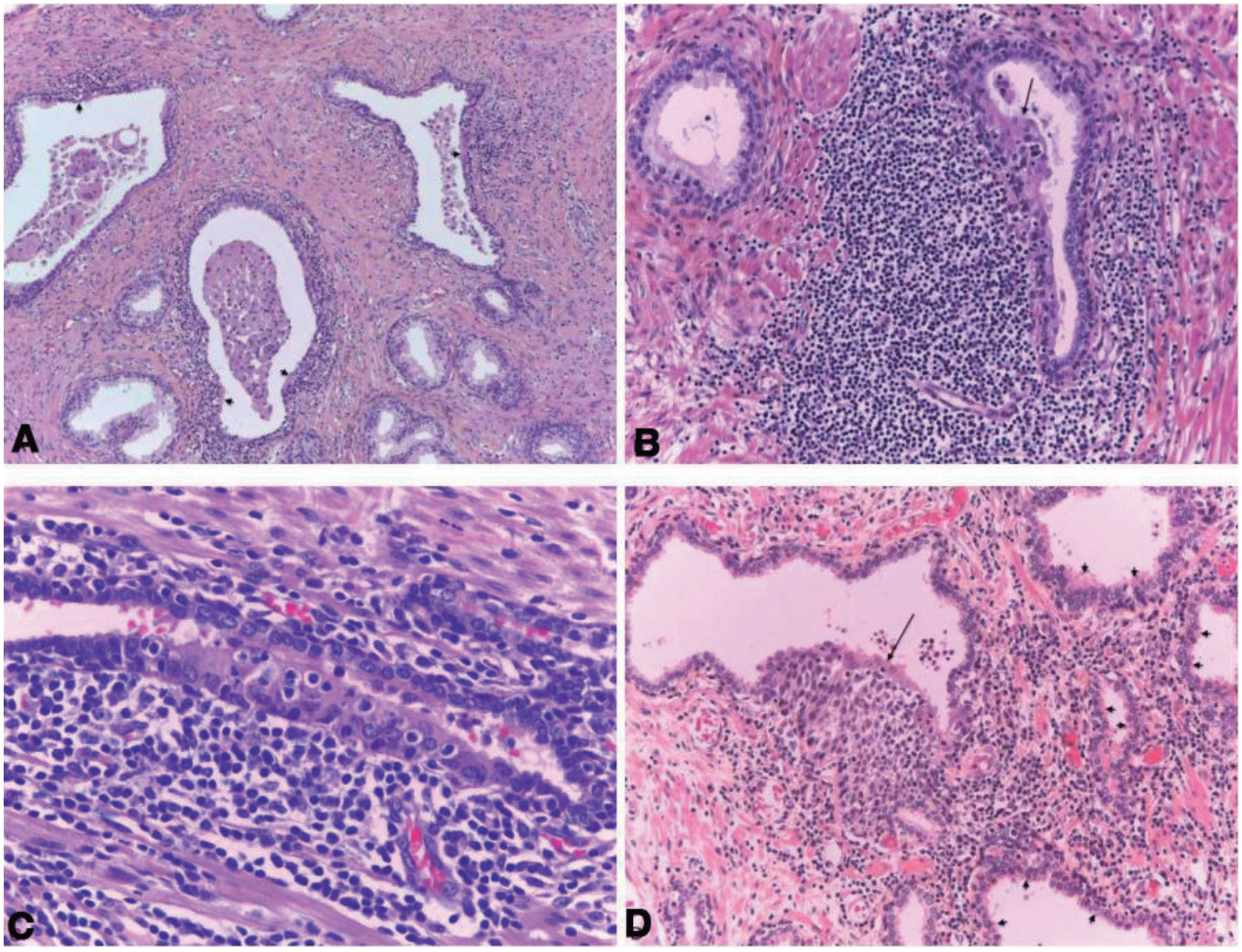

Fig. 1. Histological characteristics of prostatic LEL. **A.** Chronic prostatic inflammation with lymphocytic infiltrates involving prostatic ducts in multiple areas with LEL formation (short arrows). **B.** High grade chronic inflammation with typical LEL (arrow). **C.** General view of a typical LEL: the lymphoid cells distorting ductal eosinophilic epithelium are cytologically small and mature. **D.** LEL in area of squamous epithelial metaplasia (arrow). Note the presence of foci of eosinophilic epithelial metaplasia in the surrounding acini (short arrows). Haematoxylin-eosin-saffron. A, x 100; B, D, x 200; C, x 400.

were set: optimal tissue preservation with few or no autolysis according to light microscopic evaluation of the autopsy specimens; no data for treatment prior to prostate surgery; no evidence of a lymphoproliferative disorder in the patient's history, recorded after reviewing all available clinical, laboratory, and radiologic data; no histological features for primary prostatic lymphoma (Péricart et al., 2020). PSA was not investigated in this study due to the lack of data in the autopsied group of patients.

The age of the adult patients ranged from 19 to 88 years (mean 57.35 years). The age of the new-borns and children ranged from 1 day to 13 years (mean 2.79 years or 33.5 months). The weights of adult prostate specimens from autopsy, TURP, AD and RP- ranged respectively from 10 to 50 g (mean, 25.39 g), 7 to 50g (mean, 27.87 g), 10 to 215 g (mean, 83.12 g), and 20 to 120 g (mean, 51.23 g). The weights of autopsy new-borns and children's prostate specimens ranged from 2.7 to 10 g (mean, 5.22 g).

The study was approved by the local Ethics Committees of the hospitals.

All specimens were routinely fixed in 10% buffered formalin and embedded in paraffin for histological evaluation. Standard 4-μm-thick sections were cut from paraffin blocs. Whole mounted organ sections of RP and between 3 to 15 blocks of TURP/AD-specimens were studied. One to three whole organ sections from each autopsy prostate were examined to view the three anatomic parts of the gland (McNeal, 1968).

Retrospectively, tissue sections from each case were observed independently by two pathologists (DD and MK). Sections were stained with haematoxylin-eosin (HE) and haematoxylin-eosin-saffron (HES).

The presence of distinct morphologic changes (LEL presumably) in double-layered prostatic ductal epithelium immediately adjacent to lymphoid clusters and aggregates were analysed in qualitative and quantitative terms. The changes included the presence of a cuboidal or polygonal strongly eosinophilic epithelium compared with epithelium within the same duct, distally to the lymphoid aggregate, and clusters of three or more lymphoid cells with distortion of some epithelium (Matias-Guiu and Esquius, 1991; Daniels, 1992; Valdez et al., 2003; Isaacson et al., 2008; Giday et al., 2011).

The morphologic and quantitative analysis of the intensity of prostatic CI was performed by the use of a simplified grading system, introduced by Delongchamps, et al., 2008 based on the classification of Nickel, et al., 2001: CI of low grade (LG) and CI of high grade (HG). For cases with varying intensity of the inflammatory infiltrate, the highest grade was recorded.

Ten cases (5 with and 5 without PCa), showing distinct morphological changes in prostatic ductal epithelium and 5 cases without prostatic inflammation were selected for immunohistochemical study using the standard avidin-biotin peroxidase complex technique. The following primary antibodies (Dako, Caripenteria, California, USA, Leica Biosystems and Diagomics, France, Diagomics, France) were used: anti-cytokeratin AE1/AE3 (1:100, clone D5/16B4); anti-p63 (1:200, clone 4A4); anti-CD3 (1:150, clone SP7); anti-CD20 (1:100, clone L26); anti-epithelial membrane antigen (EMA or MUC1) (1:400, clone E29); and anti-PD-L1 (1:200, clone QR1). Tonsillar tissue from adenoidectomies served as an external positive control for PD-L1 expression.

Fisher's exact test was applied to distinguish associations among the categorical variables. A value of $P<0.05$ was considered statistically significant.

Results

Qualitative findings

In cases with prominent CI, most prostatic ducts exhibited mild to moderate dilatation, contained macrophages and exfoliated epithelial cells, and the inflammatory infiltrates often reached the ductal epithelium (Fig. 1). Prostatic ducts were involved in multiple areas (Fig. 1A) or immediately adjacent to lymphoid aggregates and follicles (Fig. 1B).

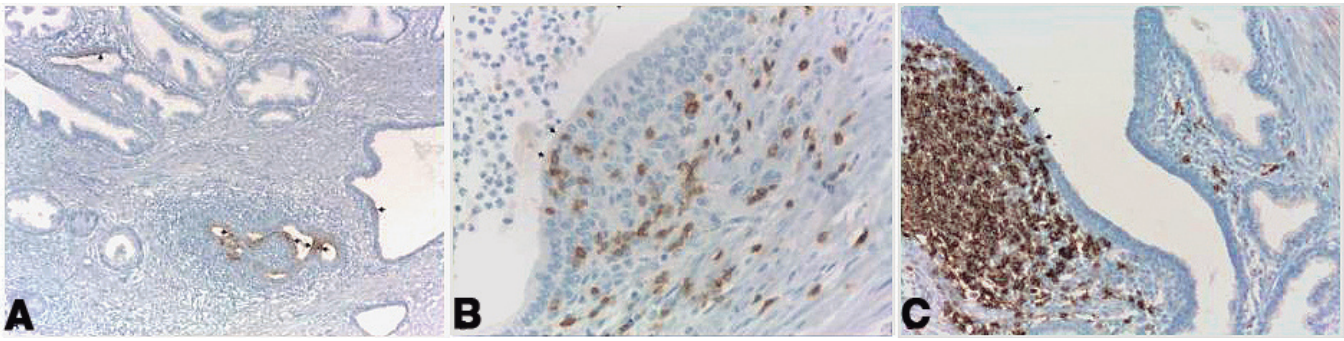

Fig. 2. Immunohistochemical characteristics of prostatic LEL. **A.** Strong diffuse cytoplasmic expression with membranous accentuation of MUC1 in LEL (short arrows), whereas the surrounding non eosinophilic secretory and basal cells are negative. The lymphoid cells that constitute LEL are most often CD3+/CD8+ T cells (short arrows) **(B)**, although a few CD20+ B cells are occasionally seen **(C)** (short arrows). Note the CD20 positivity of periductal lymph follicles. A, x 100; B, x 400; C, x 200.

Microscopically, the ductal epithelium seemed histologically different from the non-inflamed epithelium (Fig. 1): it was higher, polygonal or cylindrical, with prominent eosinophilic cytoplasmic changes (Fig. 1B,C). The suprabasal epithelial areas were reticulated. Single or clustered lymphocytes surrounded and penetrated the ductal epithelium (Fig. 1). LEL were often observed in close proximity or in combination with the foci of squamous and eosinophilic metaplasia (EM) (Fig. 1D). Immunohistochemically, LEL were easily noticeable even at low microscopic magnification after immunostaining with MUC1 (Fig. 2A). The lymphoid cells that constituted LEL were cytologically small, mature, lacked atypical morphologic features, and most of them were CD3+/CD8+ T-cells, although a few CD20+ B-cells were occasionally seen (Fig. 2B,C). Aggregates of CD20+ B were found to surround the dilated prostatic ducts (Fig. 2C). In addition, the serial sections showed strong membranous PD-L1 expression localized in the eosinophilic epithelium of LEL (Fig. 3A-D). LEL were best observed after cytokeratinAE1/AE3 immunostaining (3E). Meanwhile, their epithelium was p63 negative, surrounded by a positive basal cell reticulated layer (Fig. 3F). In the foci of HG CI, in one field of view numerous PD-L1 positive LEL can be observed (Fig. 3A), as well as among the urothelium of large peri-urethral ducts (Fig. 3F). More or less pronounced PD-L1 expression was found also in immune cells surrounding LEL (Fig. 3D,G,H) and in intra-luminal macrophages (Fig. 3B,D). In the foci with EM (Fig. 3H), as well as in the investigated 5 cases without prostatic CI, PD-L1

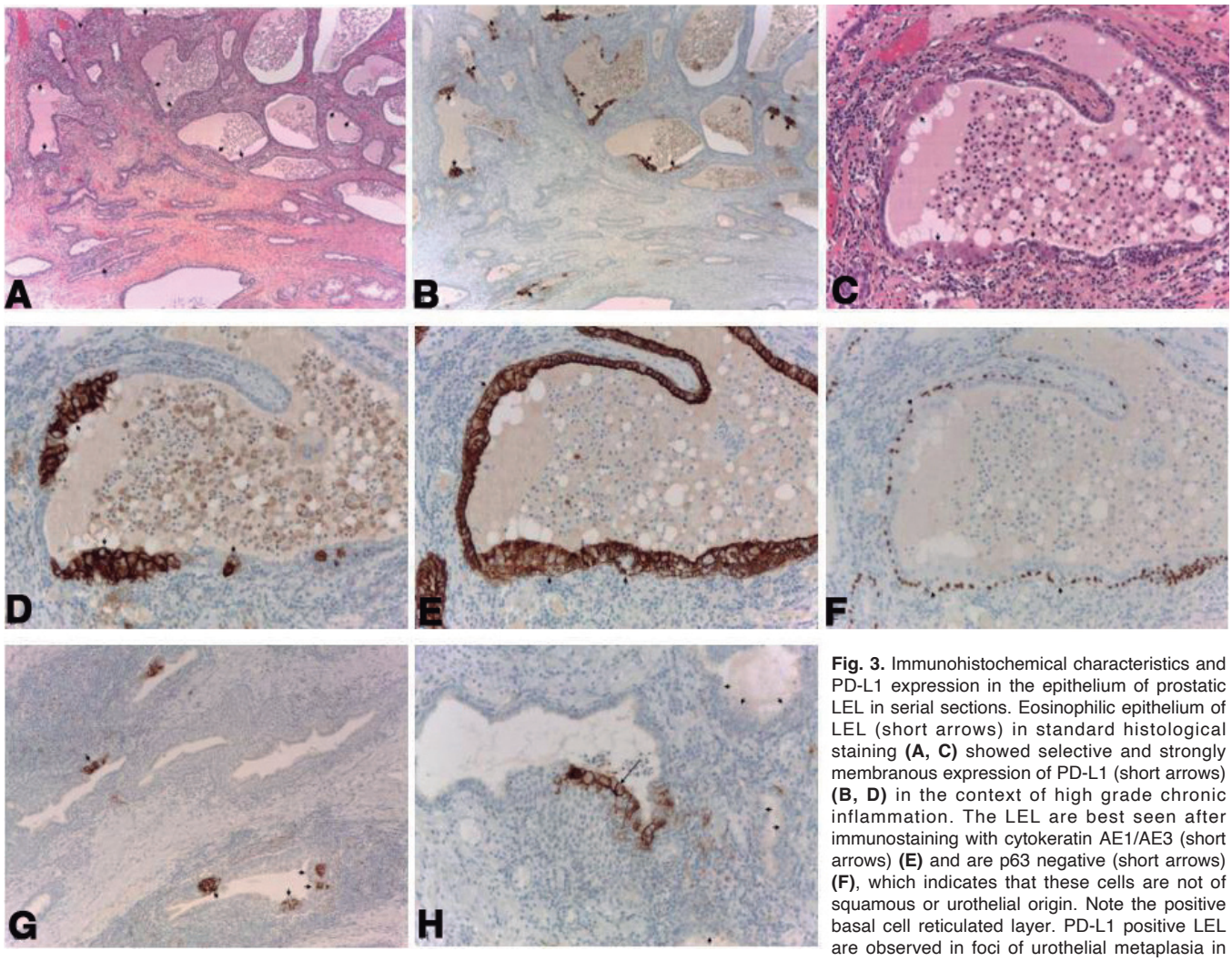

Fig. 3. Immunohistochemical characteristics and PD-L1 expression in the epithelium of prostatic LEL in serial sections. Eosinophilic epithelium of LEL (short arrows) in standard histological staining **(A, C)** showed selective and strongly membranous expression of PD-L1 (short arrows) **(B, D)** in the context of high grade chronic inflammation. The LEL are best seen after immunostaining with cytokeratin AE1/AE3 (short arrows) **(E)** and are p63 negative (short arrows) **(F)**, which indicates that these cells are not of squamous or urothelial origin. Note the positive basal cell reticulated layer. PD-L1 positive LEL are observed in foci of urothelial metaplasia in the large periurethral prostatic ducts **(G)** or in the LEL located above the foci of squamous metaplasia **(H)**. Note the negativity for the PD-L1 in the surrounding acini with eosinophilic metaplasia (short arrows) (**H**, serial section of Fig. 1D). Positive PD-L1 expression in intraluminal macrophages **(B, D)** and in surrounding immune cells of periductal lymphoid aggregates or follicles **(D, G, H)**. Haematoxylin-eosin-saffron. A, x 50; C-H, x 200.

expression was not detected (data not shown).

Quantitative findings

LEL were identified in all types of prostatic specimens examined and in all types of prostatic CI: in 78 of all 110 cases (70.9%) from patients with HP (15/78 cases or 19.2% with LG-HP and 63/78 cases or 80.8% with HG-HP); in 9/9 cases (100%) from the group of patients with NSGP; in 57/83 (68.7%) and 24/30 (80%) adjacent to BPH and PCa respectively. The statistical analysis showed a significant association of the presence of LEL and HG-CI ($p<0.001$) and failed to detect any correlation between the presence of LEL and BPH and PCa ($p=0.467$ and $p=0.243$ respectively).

LEL were not found in 47 of all 144 patients examined (32.6%): 19 patients without prostatic inflammation, including 16 autopsy medico-legal cases of young men who died in traffic accidents, 6 prostates of new-borns and children in prepuberty, and 22 cases with LG-CI.

Discussion

CI, a common finding in human prostate, has been associated with the most frequent socially important prostate diseases: prostatitis, BPH and PCa. There is epidemiological, histopathological, and molecular evidence that CI is crucial for the etiology and pathogenesis of these conditions (De Marzo et al., 2007; Delongchamps et al., 2008; Sfanos et al., 2018).

LEL in the prostate have not been described in detail so far, as we were able to find only three publications on prostatic ductal inflammatory changes in the American medical literature (Cruickshank, 1965; Blumenfeld et al., 1992; Di Carlo et al., 2007). The results of our study show that the prostatic epithelium, like other glandular locations (pancreas, salivary glands, thyroid, breast) (Daniels, 1992; Valdez et al., 2003; Isaacson et al., 2008; Giday et al., 2011), is transformed into specialized lymphoepithelium, characterized by increased cytoplasmic eosinophilia and distortion by aggregates of lymphoid cells. This constant finding is in unison with the presented histologic definition of LEL (Isaacson et al., 2008). The use of cytokeratin immunostaining emphasizes the clusters of intra-epithelial lymphocytes in the LEL as well. The epithelial ductal cells express also MUC1, typical for epithelium in LEL with other locations (Taki et al., 2002; Sung et al., 2015).

The mucosal surface of the prostate parenchyma indirectly interacts with the urethral lumen via the branched tubulo-acinar system. This gives the possibility for continuous exposure of ductal epithelial cells to intra-luminal foreign agents via the urethral way and may play an important barrier function. However, the results of our study show that prostatic ductal LEL, by themselves, have no diagnostic specificity. They can be found in all types of prostatic specimens (TURP/AD, RP, and autopsy), and in all types of prostatic CI known from the daily practice of the uropathologist: HP, NSGP, as well as in cases of reactive lymphoid infiltrates in the vicinity of BPH and PCa. On the other hand, our quantitative results show an evident connection between the incidence of LEL in CI-prostate and the degree of antigenic stimulation. Proof of this is the presence of a small amount of LEL in the group of patients with LG-CI and their significant increase in patients with HG-CI ($p<0.001$), and in 100% of cases with NSGP (HG by definition (Dikov et al., 2020). Obviously, the morphogenesis of the prostatic LEL is in direct association with the intensity of CI. None of those investigated by us, adult patients free from prostatic inflammation, new-borns and children in prepuberty, had LEL. Probably, prostatic LEL is not present in embryonic life, in newborns, children and in normal non inflammatory adult human prostate and develop only upon antigenic stimulation and/or inflammation.

Mostly CD3+/CD8+ T-lymphocytes without cytological atypia are involved in ductal prostatic epithelium of LEL. The mature polyclonal lymphoid cells show antigenic characteristics of both reactive inflammatory infiltrates in epithelial tissues and autoimmune-related inflammatory lesions (Matias-Guiu and Esquius, 1991; Daniels, 1992). It is also shown that IEL in normal and inflammatory prostate are mainly T cells (Dikov et al., 2015). In this regard the expression of PD-L1 in the LEL which we showed is a very interesting and debatable phenomenon. PD-L1 was strongly expressed in the epithelium of LEL in patients with CI, but not in normal or non-inflammatory prostate. This expression paralleled the degree of lymphocytic inflammatory infiltration like in some autoimmune diseases (Kobayashi et al., 2005). T cell inhibitory molecules, the so called immune checkpoints, limit the activation and effector function of organ-specific antigen-reactive T cells. PD-L1 expression is normally upregulated during inflammation to prevent tissue damage (Keir et al., 2008). Abnormal epithelial expression of PD-L1 has been observed in inflammatory bowel disease, *Helicobacter pylori*+ chronic gastritis, celiac disease, and salivary gland Sjöngren's syndrome (Kobayashi et al., 2005; Chulkina et al., 2020). Prostatic LEL are PD-L1 positive like these chronic inflammatory diseases and tonsillar crypts lymphoepithelium (a gold standard for external positive control in daily diagnostic practice). We can speculate that the expression of PD-L1 in LEL is an immune response aiming to prevent a persistent T cell activation leading to excessive tissue damage and autoimmune T cell-mediated prostatitis. This "adaptive or innate immune resistance" mechanism could serve as a basis for explanation of the paucity of intra-tumoral lymphocytic infiltration and PD-L1 expression in PCa, always accompanied by CI (Martin et al., 2015).

The human prostate is endowed with a lympho-epithelial component which is responsible for the genito-urinary mucosal immunity and so the concept of the

prostate-associated lymphoid tissue (PALT) was created. Our results suggest that probably LEL are formed in adult life to support local aggregation of lymphocytes in the prostate and are an integral part of HG CI and PALT (Di Carlo et al., 2007).

Further investigations are necessary to clarify the relationships of HG-CI-induced PD-L1+ LEL with peripheral prostatic immune tolerance, autoimmune genesis of prostatitis, and precancerous prostatic lesions versus PCa.

The differential diagnosis of benign prostatic inflammatory LEL should be made with marginal zone lymphomas and EM in prostatic epithelium. Primary prostatic lymphomas are exceedingly rare (0.12%), as 19% of them are MALT/lymphoplasmocytic lymphomas. They showed abundant LEL with destructive character, containing large, atypical centrocyte-like B-lymphoid cells (Pericart et al., 2020). The eosinophilic epithelial cell cytoplasm in prostatic EM (also MUC1+) (Koleva et al., 2019) was granular, the lesion being with both ductal and acinar localisation. It was not accompanied by intra-epithelial lymphocytosis and was PD-L1 negative, according to the results of the present study (Fig. 3H).

Conclusion

The novel data from this study suggest, for the first time, that PD-L1 positive LEL are a constant histological finding in prostatic CI and reflect a HG inflammatory microenvironment.

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Conflicts of Interest. The authors declare no conflict of interest.

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